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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Manuel Campos, et al.

Serial No. 09/506,078 Group Art Unit: 1648

Filed: 02/16/00 Examiner: Foley, Shanon A.

For: FUSION PROTEINS COMPRISING CARRIERS THAT CAN INDUCE A DUAL IMMUNE RESPONSE

Attorney Docket No: 3153.00205

Unsigned

DECLARATION

I, Mohamad A. Morsey, do hereby say that:

1. I am an expert in the field of animal and human health and specifically with regard to fusion proteins used in vaccine compositions, having years of experience in the field.

2. I have reviewed in detail the outstanding Office Action issued July 2, 2002. Specifically, I have reviewed the rejection of claims 1-17 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,684,145 to Van Der Zee, et al. and the Mittal, et al. reference. The rejection involves a single issue with regard to establishing a *prima facie* case of obviousness. Specifically, a fact-based explanation is needed as to why one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the strong immunogenicity of BHV-1 gD taught by Mittal, et al. with the *E. coli* fimbrial subunit portion of the hybrid protein disclosed in the Van Der Zee, et al. patent to evoke an immune response against GnRH and protect against BHV-1 infection. Based on facts well known to those of skill in the art, the present invention as claimed is patentably distinct over the prior art references because one of ordinary skill in the art would not know to produce, or have a reasonable expectation of success in producing, the claimed invention since there is no reason to believe that the combined protein would have active immunogenic sites once the strongly immunogenic BHV-1 gD is combined with the antigenic determinant of GnRH of the protein disclosed in the Van Der Zee, et al. patent.

3. The basis of my conclusion stems from information derived from my own research related to the subject invention, the specification of the present application, and from published information well known to those of skill in the art (Bosch, et al., "Effects of linker insertions on the biogenesis and functioning of the *Escherichia coli* outer membrane pore protein PhoE," Molec. Gen Genet 208:485-489 (1987)[hereinafter, "Reference 1"] and Agterberg, et al, "Outer-membrane PhoE protein of *Escherichia coli* K-12 as an exposure vector: possibilities and limitations," Gene, 88: 37-45 (1990)[hereinafter, "Reference 2"]).

4. Binding of proteins from two different sources (e.g., a first proteinaceous portion that is analogous to all or part of an endogenously-synthesized peptide to a carrier that is a proteinaceous portion analogous to all or part of an immunogen from a pathogen capable of pathogenically infecting a vertebrate) can affect or functionally alter immunogenic sites, alter structural confirmation of either or both peptides, destroy functionality of either or both peptides, or make other expected and/or unexpected alternatives that result in a non-functional and/or non-immunogenic fused protein. In other words, merely connecting any two proteins having individual functionality can be rendered non-functional once the two proteins are fused.

5. Specifically referring to the References 1 and 2, the individual function of each protein, when each protein is subsequently fused, is very unpredictable. In the references, PhoE is the studied protein. PhoE is an outer membrane protein with eight cell surface exposed regions. This protein also acts as a phage receptor. The exposed regions are predicted to serve as sites for insertion of foreign epitopes to make fusion proteins that allow display of both the epitope and the carrier (PhoE) at the cell surface, while at the same time maintain the function of PhoE protein as a phage receptor. Both References 1 and 2 prove that this prediction cannot be used to determine a priori which sites are suitable for insertion of foreign epitopes. It can be seen that insertion at some exposed sites maintain the function of PhoE as an outer membrane protein whereas insertion of

epitopes at other exposed sites interfered with assembly of PhoE into the outer membrane and its function as a phage receptor.

6. It is not obvious from the cited prior art references that an immunologically functional fusion protein can be created that preserves a protective, immune function of a carrier that is a proteinaceous portion analogous to all or part of an immunogen from a pathogen capable of pathogenically infecting a vertebrate by providing T-cell help in producing sufficient quantity and quality of antibodies against a first proteinaceous portion that is analogous to all or part of an endogenously-synthesized peptide. The cited prior art references do not disclose or suggest a functional fusion protein that includes a carrier having multiple T-cell epitopes that correspond to a high responder rate in a polymorphic population. The cited prior art references do not disclose or suggest that a fusion protein can be produced that induces a dual immune response that inhibits both the activity of a peptide endogenously synthesized by the vertebrate and inhibits a pathogenic infection in the vertebrate. Hence, the cited prior art references do not disclose nor suggest that an immunogenic, subunit protein can function as a carrier (i.e., enhancing an immune response against the analog of a endogenously-synthesized peptide or part thereof), while inducing a protective response against itself in the vertebrate in order to protect the vertebrate from infection by the pathogen.

6. There is no specific factual evidence that two specific immune responses would be directed against two specific immunogens for the reason set forth above. It is mere speculation that the combination of the strong immunogen disclosed in the Mittal, et al. reference and the *E. coli* fimbrial subunit disclosed in the Van Der Zee, et al. patent, would result in a immunologically active and functional protein capable of eliciting a specific and independent dual immunogenic response against the immunogen and the *E. coli* fimbrial subunit.

7. In view of the above, it is my opinion, based on facts well known in the art and research, that the claimed fusion protein that produces a dual immune response in a vertebrate is patentably distinct from the proteins taught in the cited prior art references. Moreover, due to the unpredictability of the

combination of combining the two peptides disclosed in the prior art references, there is no factual evidence to expect such a combination necessarily would work. Therefore, the distinctions of the present invention clearly set forth a patentable invention.

The undersigned declares further that all statements made here and of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful and false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereof.

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Mohamad Morsey

Dated: June 27, 2003